26. (Amended) The cell according to claim 16, wherein the DNA response element binds a transcriptional regulatory protein which comprises a repressor selected from the group consisting of Kruppel (KRAB), kox-1, TetR, even-skipped, LacR, engrailed, hairy (hes), Groucho(TLE), RING1, SSB16, SSB24, Tup1, Nab1, AREB, E4BP4, HoxA7, EBNA3, Mad and v-erbA

29. (Amended) The molecular switch according to claim 1 or 11, wherein said compound binding sequence is about 8 to 20 nucleotides.

30. (Amended) The cell according to claim 16, wherein said compound binding sequence is about 8 to 20 nucleotides.

REMARKS

Reconsideration of the rejections set forth in the Office Action dated October 9, 2001 is respectfully requested. Applicant petitions the Commissioner for a 3-month extension of time. A separate petition accompanies this amendment. Claims 1-19 and 21-30 are currently under examination.

I. Amendments

The specification has been amended to correct minor typographical errors.

The claims have been amended as set forth above in order to expedite the prosecution of this case. Support for the compound binding sequence being non-native in claims 1, 11 and 18, can be found in the specification on at least page 53, lines 3-5; page 55, lines 35-36; and page 59, lines 21-23.

Claims 1, 11 and 18 have also been amended to clarify that the compound binding site is the same as, overlapping, or adjacent to the DNA response element. Support for this amendment may be found in the specification on at least page 16, lines 18-19 and page 16, lines 25-26.

Claims 23-26 have been amended to clarify that the DNA response element binds a transcriptional regulatory protein which comprises either an activator (claims 23 – 24) or repressor (claims 25 – 26). Support for these amendments may be found in the specification on at least page 22, line 13 – page 23, line 23.

None of the other claim amendments introduces a substantive limitation. No new matter

has been added by these amendments.

Also attached is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with Markings to Show Changes Made."**

II. Rejection Under 35 U.S.C. §112, first paragraph

Claims 1-19 and 21-30 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleges that the specification does not reasonably provide enablement for a molecular switch comprising a first nucleic acid construct containing a DNA response element for any transcriptional regulatory protein operably linked to a first promoter, a compound binding sequence in the vicinity of the DNA response element, a transgene under the control of the first promoter and any DNA binding compound, a cell comprising the molecular switch, and a method of producing a cell having the molecular switch.

This rejection is traversed in view of the following arguments.

A. Legal Standard

Under 35 U.S.C. §112, a patent specification which contains a teaching of how to make and use the invention must be taken as enabling unless the PTO provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 U.S.P.Q. 367, 369-70 (C.C.P.A. 1971).

The claimed invention disclosed in the specification cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte Linn,* 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald,* 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959) (emphasis added). The number and variety of examples is irrelevant if the disclosure is "enabling" and set forth the "best mode contemplated." Even in an unpredictable art, Section 112 does not require disclosure of a test of every species encompassed by the claims. *In re Angstadt,* 190 U.S.P.Q. 214, 218 (CCPA 1976).

An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech Inc,* V. *Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically

engages in such experimentation. *ML T. v A.B. Fortia,* 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands, 858* F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); *In re Jackson, 217 U.S,P.Q.* 804, 807 (PTO Bd. Pt. App. Int. 1982) (emphasis added). Finally, the Examiner has the burden of showing that the disclosure entails undue experimentation. *In re Angstadt, 537* F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976) (emphasis added).

B. Meeting the Legal Standard

According to the accepted standards of enablement set out above, an invention is enabled if one skilled in the art could make and use the claimed invention without undue experimentation.

How-to-make requirement. With respect to the molecular switch of claim 1, the specification teaches one of skill in the art how to make a nucleic acid construct having (i) a DNA response element for a transcriptional regulatory protein operably linked to a promoter; (ii) a non-native compound binding sequence for binding to a DNA binding compound; and, (iii) a transgene under the control of the promoter. In particular:

The specification discloses representative DNA response elements at, for example, page 23, line 42 – page 24, line 11.

Exemplary transcriptional regulatory proteins are described, at least, on page 21, line 15 – page 23, line 25.

A number of exemplary promoters in accordance with the invention are disclosed on, at least, page 24, line 13 – page 26, line 19.

Several exemplary DNA binding compounds are disclosed on, at least, page 29, line 38 – page 31, line 19.

Exemplary transgenes are disclosed on, at least, page 27, lines 18 – 41.

Exemplary host cells are disclosed on, at least, page 28, line 7 – 13.

The specification teaches a variety of methods for delivery of the nucleic acid constructs into host cells at, for example, page 28, line 14 – page 29, line 36.

Further in support of Applicants' position, the Examiner has provided no basis for believing that one skilled in the art could not make the invention as claimed without undue experimentation.

How-to-use requirement. The how to use requirement is met if the invention as claimed,

including the scope of transcriptional regulatory proteins, promoters, DNA binding compounds, and host cells, would be reasonably expected to result in a molecular switch for modulating gene expression.

A number of exemplary nucleic acid constructs that contain a variety of DNA response elements, promoters, and transgenes were tested for gene expression modulation with a number of transcriptional regulatory proteins and DNA binding compounds. The data presented in the examples on pages 53 – 66 of the specification demonstrate that gene expression modulation is achieved using representative DNA binding compounds which bind to compound binding sequences in the vicinity of a number of DNA response elements for a variety of transcriptional regulatory proteins.

Based on these studies, Applicants submit that there is a reasonable expectation that nucleic acid constructs produced in accordance with the present invention, including any DNA binding compound which binds to a compound binding sequence in the vicinity of a DNA response element for a transcriptional regulatory protein, in a variety of different host cells, would successfully modulate gene expression of any transgene.

Further in support of Applicants' position, the Examiner has provided no basis for believing that one skilled in the art could not use the invention as claimed without undue experimentation. After reciting that the sequence binding preferences for some DNA binding compounds are not disclosed, the Examiner simply concludes that more guidance is needed as to the elements discussed above, and more experimentation is needed to assess the effect of these components on gene expression in the molecular switch. However, as noted above, the invention cannot be questioned on the unsupported skepticism of the Examiner. Moreover, if the DNA binding activity of a candidate compound is not known it may be evaluated in a pre-screening assay, as described on, at least, page 30, lines 9 – 10 and page 37, line 16 – page 38, line 5.

For the reasons presented above, Applicants submit that the specification teaches one of skill in the art how to make and use the invention as presently claimed without undue experimentation and that the rejection of the claims based on the enablement requirement of 35 U.S.C. §112, first paragraph, should therefore be withdrawn.

III. Rejection Under 35 U.S.C. §112, second paragraph

Claims 1-19 and 21-30 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the

applicant regards as the invention. These rejections are traversed in view of the following.

The Examiner alleges the phrase "a DNA binding compound" renders the claims indefinite because "[I]t is unclear what compound is as to a DNA binding compound." The Examiner has the burden of providing a specific rejection of claim terminology and reasons why the Examiner believes the terminology is indefinite or would not readily be understood by those of skill in the art. *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), *cert. dismissed*, 474 U.S. 976 (1985). Definiteness of claim language must be analyzed not in a vacuum, but in light of such elements as (1) the content of the particular application disclosure, (2) the claim interpretation that would be given by one of ordinary skill in the pertinent art at the time the invention was made, and (3) the teachings of the prior art. *In re* Wiggins, 488 F.2d 538, 179 USPQ 421, 423-24 (C.C.P.A. 1973). Applicants direct the Examiner's attention to page 29, line 38 – page 31, line 19 of the specification, which disclose DNA binding compounds. Furthermore, the prior art describes a number of DNA binding compounds that bind to double stranded DNA at sites in the vicinity of regulatory binding sequences. See, for example, U.S. Pat. Nos. 5,306,619, 5,693,463, 5,716,780, 5,726,014, 5,744,131, 5,738,990, 5,578,444, and 5,869,241 which are incorporated by reference on page 16, lines 12 – 14 of the specification. Thus, Applicants submit that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would be able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the phrase "a DNA binding compound."

The Examiner also alleges that the phrase "in the vicinity of said DNA response element" renders the claims indefinite because it is unclear where a compound binding site is located with respect to the DNA response element. Claims 1, 11 and 18 have been amended to clarify that the compound binding site is the same as, overlapping, or adjacent to the DNA response element. Support for this amendment may be found in the specification on, at least, page 16, lines 18-19 and page 16, lines 25-26. Claims 2-10, 12-17, 19 and 21-30 are dependent on amended claims 1, 11 and 18.

Claims 1-17 and 21-30 have been rejected as indefinite because it is not clear how a DNA binding compound can be part of a nucleic acid construct. Claims 1 and 11 have been amended to remove the numeral "iv", thus making it clear that the DNA binding compound is part of the molecular switch, not the nucleic acid construct. Claims 2-10, 12-17, and 21-30 depend from claims 1 and 11.

Claim 10 is rejected as indefinite for the use of the term "adeno-associated virus vector."

In rejecting a claim under the second paragraph of 35 U.S.C. 112, it is incumbent on the Examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims. *Ex parte* Wu, 10 USPQ 2d 2031, 2033 (B.P.A.I. 1989). The Examiner is directed to page 38, lines 28-29 of the specification, which lists references showing that adeno-associated virus vectors are well known to those of skill in the art. Thus, Applicants submit that : (i) the Examiner has not provided any reasoning as to why the claim is unclear when read in view of the specification, and (ii) when read in light of the supporting specification, the phrase "adeno-associated virus vector" is sufficiently definite.

Claim 23 is rejected as indefinite for lacking sufficient antecedent basis for the use of the phrases "said regulatory domain" and "an activator domain." Claim 23 has been amended to clarify that the DNA response element binds a transcriptional regulatory protein which comprises an activator domain. Support for this amendment may be found in the specification on, at least, page 22, lines 17 – 20.

Claims 14, 29 and 30 are rejected as indefinite for the use of the term "from about ... to ..." Each of the claims has been amended is accordance with the Examiner's suggestion by removing the term "from."

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

IV. Rejection under 35 U.S.C. §§102(a) and 102(b)

Claims 1, 3, 5 and 16-17 were rejected under 35 U.S.C. §102(b) as being anticipated by Voet *et al.* (Biochemistry pages 854-856 and 868 (1990)).

Claims 1, 3, 5 and 16-18 were rejected under 35 U.S.C. §102(b) as being anticipated by Gottesfeld *et al.* (Nature 387, 202-205 (1997)).

Claims 1-5, 8 and 16-17 are rejected under 35 U.S.C §102(b) as being anticipated by Evans *et al.* (U.S. Patent 5,071,773).

Claims 1, 3, 5 and 16-18 are rejected under 35 U.S.C. §102(a) as being anticipated by Dickinson *et al.* (Proc. Natl. Acad. Sci. USA 95, 12890-12895 (1998)).

These rejections are respectfully traversed in view of the foregoing claim amendments and following remarks.

A. Legal Standard for Anticipation.

For a prior art reference to be anticipating under 35 U.S.C. §102, it must teach "each and every" element of the claimed invention. *In re Bond,* 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). "Anticipation requires identity of invention: the claimed invention, as described in appropriately construed claims, must be the same as that of the reference, in order to anticipate." *Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc.*, 33 USPQ2d 1496 (Fed. Cir. 1995).

Applicants submit that none of the cited references meets the legal standard of anticipation for the reasons set forth below.

B. Claim Limitations of the Presently Claimed Invention

The present invention, as embodied in amended claim 1, includes the following claim elements:

1. A nucleic acid construct having:

(a) a DNA response element for a transcriptional regulatory protein operably linked to a first promoter;

(b) a non-native compound binding sequence which is the same as, overlapping, or adjacent to said DNA response element for binding to a DNA binding compound;

(c) a transgene under the control of said first promoter; and

2. The DNA binding compound.

C1. Rejection over Voet *et al.*

Voet *et al.* disclose the *E. coli lac* system wild-type genes β-galactosidase, galactoside permease, and thiogalactoside transacetylase, which are contiguously arranged on the *E. coli* chromosome. *lac* repressor is capable of inhibiting the synthesis of the *lac* operon proteins. Nowhere does Voet *et al.* show or suggest:

(i) a DNA binding compound which is distinct from the transcriptional regulatory protein;

(ii) a non-native compound binding sequence; or

(iii) a transgene, which is defined in the specification on page 10, lines 3-6 as "the portion of a heterologous nucleic acid construct, expression cassette or vector which comprises the coding sequence for a polypeptide, wherein the gene is associated with other components, *i.e.*, the promoter with which it is not normally associated in nature. The genes described in Voet *et al.* are all associated with their native promoters, and are therefore not transgenes.

Thus, Voet *et al.* does not disclose each and every element of the invention, and therefore cannot anticipate the presently claimed invention.

C2. Rejection over Gottesfeld *et al.*

Gottesfeld *et al.* discloses small molecules that target specific DNA sequences for controlling gene expression. The reference discloses an eight-ring polyamide targeted to a specific region of the transcription factor TFIIIA binding site which interferes with 5S RNA gene expression in *Xenopus* kidney cells. Nowhere does Gottesfeld *et al.* show or suggest a transgene. The 5S RNA gene, as described in Gottesfeld, is associated with its native promoter, and is therefore not a transgene as defined by the present invention. The reference also fails to disclose a non-native compound binding sequence.

Thus, Gottesfeld *et al.* does not disclose each and every element of the invention, and therefore cannot anticipate the presently claimed invention.

C3. Rejection over Evans *et al.*

Evans *et al.* discloses two hormone receptor-related bioassays. According to the reference, cells that contain a non-endogenous DNA which expresses a protein suspected of being a hormone receptor and which contain a DNA sequence encoding a hormone response promoter/enhancer element linked to an operative reporter gene, are cultured. A hormone, when complexed with the hormone receptor, can bind to the hormone response promoter/enhancer element (column 12, lines 11-16). The hormone does not directly bind to a DNA binding sequence. Nowhere does Evans *et al.* show or suggest a DNA binding compound that is distinct from a transcriptional regulatory protein. The reference also fails to disclose a non-native compound binding sequence.

Thus, Evans *et al.* does not disclose each and every element of the invention, and therefore cannot anticipate the presently claimed invention.

C4. Rejection over Dickinson *et al.*

Dickinson *et al.* discloses two pyrrole-imidazole polyamides that bind DNA sequences immediately adjacent to the binding sites for the transcription factors Ets-1, lymphoid-enhancer binding factor 1, and TATA-box binding protein. Nowhere does Dickinson *et al.* show or suggest a non-native compound binding sequence which is the same as, overlapping, or adjacent to said

DNA response element for binding to a DNA binding compound.

Thus, Dickinson *et al.* does not disclose each and every element of the invention, and therefore cannot anticipate the presently claimed invention.

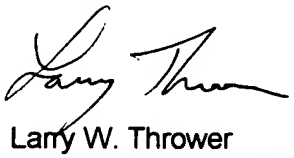
Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

V. Conclusion

In view of the above remarks, the applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4405.

Respectfully submitted,



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Version with Markings to Show Changes Made

In the Specification:

The paragraph beginning on page 7, line 42, has been replaced with the following rewritten paragraph:

Figure 4B depicts the effect of various concentrations of 21x on reporter expression in *E. coli* strains that carry *rrnB* P1 promoter constructs (the sequences for which are presented in Fig. [9A] 4A), fused to a *lacZ* reporter on the chromosome as a phage mono-lysogen, as indicated in the figure. Cells were incubated with or without 21x for 24 hrs and promoter activities assayed following treatment. Promoter activities are expressed as a percentage of basal promoter activity. All samples were in triplicate, the error bars represent standard errors of the mean (SEM) for three separate experiments.

The paragraph beginning at line 24 of page 15 has been amended as follows:

None of the aforementioned regulatable expression systems exhibit all the features of an effective regulatable gene expression system. The TetR system lacks pharmacokinetics necessary for a tightly controlled system. In addition, systems such as TetR are not applicable to agricultural applications, in that it is not practical for an inducer (*i.e.* tetracycline) to be [spayed] sprayed on an entire field of plants.

In the Claims:

Claims 1, 11, 14, 18, 23-26 and 29-30 have been amended as follows:

1. (Amended) A molecular switch, comprising:
a first nucleic acid construct having

(i) a DNA response element for a transcriptional regulatory protein operably linked to a first promoter;

(ii) a non-native compound binding sequence [in the vicinity of] which is the same as,

overlapping, or adjacent to said DNA response element for binding to a DNA binding compound;

(iii) a transgene under the control of said first promoter; and

[(iv) a] the DNA binding compound.

11. (Amended) A molecular switch, comprising:

a first nucleic acid construct having

(i) a DNA response element for a transcriptional regulatory protein operably linked to a regulatable promoter;

(ii) a non-native compound binding sequence [in the vicinity of] which is the same as, overlapping, or adjacent to said transcriptional regulatory protein DNA response element for binding to a DNA binding compound;

(iii) a transgene and the coding sequence for a transcriptional regulatory protein under the control of said regulatable promoter; and

[(iv) a] the DNA binding compound.

14. (Amended) The molecular switch according to claim 1 or 11, wherein compound binding sequence has [from] about 8 to 20 nucleotides.

18. (Amended) A method of producing a cell having a molecular switch for modulating gene expression, said method comprising:

(i) transforming said cell with a nucleic acid construct having a DNA response element which binds a transcriptional regulatory protein operably linked to a promoter, a non-native compound-binding sequence [in the vicinity of] which is the same as, overlapping, or adjacent to said DNA response element for binding to a DNA binding compound, a transgene under the control of [a] the promoter; and

(ii) exposing said transformed cell to a DNA binding compound,

wherein binding of the DNA binding compound to said compound binding sequence is effective to inhibit binding of a transcriptional regulatory protein to the DNA response element, thereby derepressing or deactivating expression of the gene, where the transcriptional regulatory protein is a repressor or activator protein, respectively.

23. (Amended) The molecular switch according to claim 1 or 11, wherein said [regulatory domain is an] DNA response element binds a transcriptional regulatory protein which comprises

an activator domain selected from the group consisting of VP16, NF-κB, Gal4, TFE3, ITF1, Oct-1, Sp1, Oct-2, NFY-A, ITF2, c-myc, and CTF.

24. (Amended) The cell according to claim 16, wherein the DNA response element binds a [regulatory sequence of said of said] transcriptional regulatory protein [is] which comprises an activator selected from the group consisting of VP16, NF-κB, Gal4, TFE3, ITF1, Oct-1, Sp1, Oct-2, NFY-A, ITF2, c-myc, and CTF.

25. (Amended) The molecular switch according to claim 1 or 11 wherein the [regulatory sequence of said of said] DNA response element binds a transcriptional regulatory protein [is] which comprises a repressor selected from the group consisting of Kruppel (KRAB), kox-1, TetR, even-skipped, LacR, engrailed, hairy (HES), Groucho (TLE), RING1, SSB16, SSB24, Tup1, Nab1, AREB, E4BP4, HoxA7, EBNA3, Mad and v-erbA.

26. (Amended) The cell according to claim 16, wherein the [regulatory sequence of said of said] DNA response element binds a transcriptional regulatory protein [is] which comprises a repressor selected from the group consisting of Kruppel (KRAB), kox-1, TetR, even-skipped, LacR, engrailed, hairy (hes), Groucho(TLE), RING1, SSB16, SSB24, Tup1, Nab1, AREB, E4BP4, HoxA7, EBNA3, Mad and v-erbA.

29. (Amended) The molecular switch according to claim 1 or 11, wherein said [compound-binding] compound binding sequence is [from] about 8 to 20 nucleotides.

30. (Amended) The cell according to claim 16, wherein said [compound-binding] compound binding sequence is [from] about 8 to 20 nucleotides.